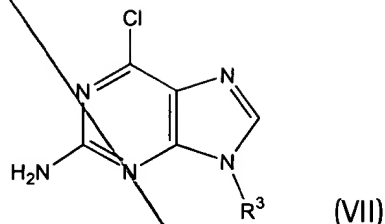
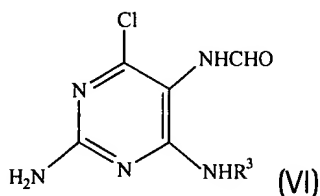




E<sup>3</sup>  
cont



wherein R<sup>3</sup> is a C<sub>2-8</sub> hydrocarbonyl group, wherein carbon atoms may be substituted by one or more heteroatoms and wherein such C<sub>2-8</sub> hydrocarbonyl group may be optionally substituted with C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, hydroxyl or protected hydroxyl, azido, phosphonyl, or halogen; provided that such groups are not attached by a glycosidic bond, comprising reacting a compound of formula (VI)



wherein R<sup>3</sup> is as defined above, with a trialkylorthoformate in the presence of an aqueous acid.

#### REMARKS

In an Office Action mailed January 28, claims 9, 18 - 20 are pending and all claims stand rejected. Claims 21 and 22 have been added. Support for claim 21 is provided at page 10 of the specification. Support for claim 22 is provided at pages 10-11 of the specification.

Claims 9 and 18 - 22 are pending.

The amendment was made in order to clarify the claims.



Claims 9, and 18 - 20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In response to the Examiner's specific points:

1. The Examiner correctly notes that hexose is not present. For example, amines such as 1-aminoribose are excluded.
2. The language, "such as" has been deleted as requested by the Examiner.
3.  $-PO(OH)_2$  is intended.
4. Support for the term "heterocycle" is found at page 10 of the specification, where the number and nature of the heteroatoms is specified.
5. The second word "atom" has been deleted because it is redundant.
6. Applicants submit that the claim amendments address the Examiner's concern with respect to the definition of  $R^3$ .
7. Benzyl is permitted. Support for substituted  $R^3$  substituents can be found in the specification at page 10.

Applicants believe that claims 9 and 18-20 as amended address the Examiner's objections. Applicants respectfully request withdrawal of the rejection of claims 9 and 18-20 under 35 U.S.C. §112.

Claims 9, and 18-20 are rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,087,697 (Daluge) in view of U.S. Patent No. 4,916,224 (Vince) or U.S. Patent No. 5,049,671 (Daluge) further in view of Norbeck, Vince, Borthwick or Shealy. Applicants respectfully traverse the rejection. The Examiner contends that the "sole difference" between the art of record and the claimed process is that "while the prior art does the reaction with the amine protected (with  $R^3$ ), the claimed process is done with the amine not protected." The Examiner further contends that "applicants must establish differences by direct, side by side comparisons and demonstrate that these differences are unexpected." Applicants respectfully point out that these differences are found in the art of record.

The Norbeck compound (Col. 1, 13) contains two unprotected amino groups at position 2 and 5 of the pyrimidine ring. Example 1, Step G of Norbeck describes a synthesis that results in



the formation of three products which are separated by column chromatography. Thus, the Norbeck process results in mixtures of compounds. This combined with separation by column chromatography renders this process unsuitable for large-scale manufacture and formulation.

The Borthwick compound (intermediate VI) contains an unprotected amino group at position 2 of the pyrimidine ring. Example 15 (bridging paragraph between col 17 and 18) describes a synthesis that results in "sticky foam" and "red filtrate". Thus, the Borthwick process results in a product with contaminants which renders this process unsuitable for large-scale manufacture and formulation.

The Shealy compound (Formula V) contains two unprotected amino groups at positions 2 and 5 of the pyrimidine ring and Example 1 describes a synthesis that results in "red syrup", "dark red syrup", yield of 52% for the first crop and 43% for the second crop. Thus, the Shealy process results in contaminants which renders this process unsuitable for large-scale manufacture and formulation.

Compounds of the '671 reference differ from those of the instant application in that the former compounds lack a chloro group at the 4 position of the pyrimidine ring and a formyl group at the 5 position. The previously-described routes to intermediates such as 6b of the '224 reference are longer, and the number of steps to the purine targets after incorporation of the group R<sup>3</sup> is greater (instant specification at page 13). Triaminopyrimidine intermediates such as 6b are air- and light- sensitive and extremely difficult to purify due to their polarity and metal-chelating abilities (specification at page 13).

Processes described in U.S. Patent No. 5,763,607 (Vince) use pyrimidine intermediates with unprotected amino groups at position 2 and 5 of the pyrimidine ring. Disadvantages are as described above: purification by column chromatography (e.g. Example 5) and/or low yield (e.g. Example 6).

The substituent at the two position of the pyrimidine ring of the '697 compounds, designated NR<sup>3</sup>, represents an amino group bearing a protecting group, e.g. an acyl group such as a C<sub>1-6</sub>alkanoyl group, e.g. formyl, acetyl or isobutyryl. One skilled in the art would realize that chloro groups are so reactive to displacement that deprotection of the amino groups leads to hydrolysis. That is, one skilled in the art would know that removal of the amino-protecting



groups before closure of the pyrimidine ring to a purine ring causes the molecule to fall apart (see specification at page 2 regarding the "extensive decomposition of the 2,5-diamino-4,6-dihydroxypyrimidine to tars").

In contrast, to these processes and intermediates, the claimed process results in a white powder at high yield, with no contaminants (see Example 8). Processes prior to the present invention, for example the '697 process, used intermediates that were protected at the 2 position because a way of making the de-protected compounds without resulting tars or hydrolysis was not known. Therefore, the process of the present invention achieved a surprising result, that is, the synthesis of chloropurine intermediates and 9-substituted 2-aminopurines in high yield and without tars or contaminants.

The '697 reference does not teach the removal of the protecting group until after ring closure to form the purine, because deprotection before ring closure causes the compound to fall apart. The secondary references describe processes that are fraught with problems of mixtures, contaminants and poor yield. In order for a §103 rejection to be proper, the combined references must suggest the claimed modification. The '697 reference in view of the secondary references clearly does not suggest the claimed modification because, as discussed above, it would not occur to one skilled in the art that such a modification could be made with success. Therefore, Applicants respectfully submit that the rejection under §103 is improper and should be withdrawn.

Claim 9 is rejected under 35 U.S.C. §103 as being unpatentable over EP 413544 in view of Norbeck, Vince, Borthwick or Shealy. As noted in the response dated November 10, 1998, the compounds of EP413 544 are outside the scope of the instant application. The 5-formamido intermediates and ring closure process of the instant specification exclude amines in which the carbon substituted by the nitrogen is also substituted by an oxygen (for example, 1-aminoribose) because these amines are unstable under the conditions required for condensation of the amine with the dichloropyrimidines. Applicants submit that this clarifies and corrects Applicants' previous remark regarding exclusion of "amines where R<sup>3</sup> is OR or OH". R<sup>3</sup> can be OR or OH, but R<sup>3</sup> cannot be unstable amines as described above. Furthermore, the process of EP 413544 is not performed by reacting a compound of formula VII of the reference with alkylorthoformate in



aqueous acid. The EP 413544 process results in complex mixtures, decomposition, the necessity for harsh conditions, and low yields (see Example 1 of EP413544). Norbeck, Vince, Borthwick and Shealy are discussed above. In contrast to the EP 413544 process and those processes and intermediates described in the secondary references, the claimed process results in a white powder at high yield, with no contaminants (see Example 8). EP 413544 does not teach the use of acid together with orthoformate and since the process results in complex mixtures, decomposition and low yields, it is unsuitable for large-scale manufacture and formulation. The secondary references do not suggest the benefits of using the intermediates of Formula VI. In order for a §103 rejection to be proper, the combined teachings must suggest the benefits of making the claimed modification. EP 413544 in view of the secondary references clearly does not suggest the claimed modification because, as discussed above, it would not occur to one skilled in the art that such a modification could be made with success. Therefore, Applicants respectfully submit that the rejection under §103 is improper and should be withdrawn.

Claims 9, 18-20 are rejected under 35 U.S.C. §103 as being unpatentable over Norbeck, Vince, Borthwick or Shealy in view of EP 413544 or Daluge '697. As discussed above, the references describe processes using intermediates in which either the 2-position and 5-position of the pyrimidine ring are unprotected (Norbeck, Vince, Borthwick, Shealy, with resulting difficulties as described above) or in which the 2-position and 5-position are protected (Daluge, with resulting difficulties as described above). The compounds of EP413544 are, as discussed above, outside the scope of the present invention, and furthermore, involve a synthetic route which leads to difficulties as described above. In order for a §103 rejection to be proper, the combined teachings must suggest the benefits of making the claimed modification. Norbeck, Vince, Borthwick and Shealy in view of EP 413544 clearly do not suggest the claimed modification because, as discussed above, it would not occur to one skilled in the art that such a modification could be made with success. Therefore, Applicants respectfully submit that the rejection under §103 is improper and should be withdrawn.



In view of the amendments and the foregoing discussion, it is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

A handwritten signature in cursive script, reading "Karen L. Prus".

Karen L. Prus, Ph.D.  
Attorney for Applicant  
Reg. No. 39,337

Date:

*July 28, 1999*

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